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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,502	05/18/2001	Michel Sadelain	MSK.P-040	1539

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/06/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,502	SADELAIN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *7-16 and 21-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,7,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to Comply

Notice to Comply With Sequence Rules	Application No.	Applicant(s)	
	09/786,502	SADELAIN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

X 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 8230, May 1, 1990.

X 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

X 3. A copy of the "Sequence Listing" in Computer Readable Form (CRF) has not been submitted as required by 37 C.F.R. 1.821(e).

___ 4. A copy of the "Sequence Listing" in Computer Readable Form (CRF) has been submitted. However, the content of the CRF does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

___ 5. The Computer Readable Form (CRF) that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute CRF must be submitted as required by 37 C.F.R. 1.825(d).

___ 6. The paper copy of the "Sequence Listing" is not the same as the Computer Readable Form (CRF) of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

___ 7. Other: _____

Applicant Must Provide:

X An initial or substitute copy of the **CRF** "Sequence Listing".

X An initial or substitute **paper copy** of the "Sequence Listing", as well as an amendment directing its entry into the specification.

X A statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support (SIRA)
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-6 and 17-20, in Paper No. 11, filed November 5, 2002, is acknowledged. The traversal is on the ground(s) that the restriction requirement is improper under the PCT rules for lack of unity. This is not found persuasive because, PCT rules for lack of unity do not allow for examination of multiple products, but instead for one product, a method of use and a method of making. In the instant case, the first product is that of group I, drawn to a fusion receptor protein that is a separate and distinct product from the nucleotide sequence that can be used to encode for the protein. The claims of group II are grouped together, because they relate to a second product, which is a nucleic acid, a method of use, host cells and expression vectors comprising the nucleic acid.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-32 are pending.

Claims 7-16 and 21-32, drawn to non-elected inventions, are withdrawn from consideration.

Claims 1-6 and 17-20 are examined on the merits.

Specification

3. The specification is objected to for not complying with the sequence rules. This application contains sequence disclosures that are encompassed by the definitions for nucleotide

and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant's attention is drawn to pages 9, 10, and 15, which contain sequences that are not listed in a separate sequence listing. Applicant should check the specification for any other examples of sequences that are not listed in a separate sequence listing.

Applicant is given the time period for reply to this office action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

4. Claims 1-6 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of the phrase "PSMA-scFv represents a single chain antibody". Amendment to "PSMA-scFv is a single chain antibody" is suggested.

Claim 1 is indefinite in view of the phrase "the connector is a region of one or more amino acids". Replacement of this phrase with the following is suggested: "the connector comprises one or more amino acids"

Claim 4 is indefinite because it refers to specific amino acid residues without a reference a specific amino acid sequence having a sequence identifier. Amendment to include an amino acid sequence having a sequence identification number is suggested. Claim 4 is also indefinite because it is not clear what is meant by the phrase "the cytoplasmic domain is a portion of CD28 cDNA spanning amino acids 336-663." First, claim 4 appears to be drawn to a polypeptide, so it is not clear if applicant intended that the cytoplasmic domain to be characterized as "a portion of CD28 cDNA", which refers to a nucleic acid. Also, how does a cDNA "span" a segment of amino acids. Secondly, after reading the Krause reference of the IDS, it is noted that the numbers of 336-663 are reference numbers for nucleic acids and not for amino acids.

5. Claims 3-5, and 18-20 and rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fusion receptors that comprise CD28 cytoplasmic domains or 4-1BB cytoplasmic domains, does not reasonably provide enablement for fusion receptors wherein the cytoplasmic domains are derived from either CD28 or 4-1BB. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 3-5 and 18-20 are rejected as not being enabled for the full scope of the invention because the recitations describing the cytoplasmic domain portion of the claimed fusion proteins is broader than what is taught in the specification.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Because of the recitation in the claims, "wherein the cytoplasmic domain is derived" from either CD28 (or is portion of CD28, where the portion is not adequate characterized) or 4-1BB, the claims are interpreted to read on fusion proteins comprising cytoplasmic domains that are not structurally characterized. The specification confines its descriptions to fusion proteins comprising art-known cytoplasmic domains, and fails to provide teachings on how to modify those domains. Because of the broad language, "derived from", the fusion proteins encompass cytoplasmic domains that have been modified from what is taught in the art. However, the specification fails to teach which amino acids or which regions are important for modification. Thus, the full scope of the claimed inventions is not supported by the specification.

This rejection may be overcome by amending the claims to recite that the cytoplasmic domain is a CD28 cytoplasmic domain or a 4-1BB cytoplasmic domain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-4 rejected under 35 U.S.C. 103(a) as being unpatentable over Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998) and further in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995).

Claims 1-4 are drawn to fusion protein compositions that comprise an scFv that binds to PSMA connected to a cytoplasmic domain of a molecule that functions as a transducer of a mammalian immune response in the presence of a costimulatory factor. The scFv may be

connected to the cytoplasmic domain by a connector (connector is optional). The cytoplasmic domain may be a ζ-chain of CD3, or may be derived from CD28.

Eshhar teaches chimeric receptors that comprise an scFv that binds a tumor antigen connected to a cytoplasmic domain such as that of a ζ-chain of CD3, or a cytoplasmic domain of CD28 (see page 3, para. 24; para. 19; page 2, para. 17 ; page 11, para. 99). Between the scFv and the cytoplasmic domain is a transmembrane domain, which is interpreted to be a linker (page 1, para 7). Thus, Eshhar teaches constructs that have an scFv that binds a tumor antigen linked to a cytoplasmic domain via a linker.

Eshhar fails to teach a chimeric receptor having an scFv that binds PSMA. However, antibodies to PSMA are known in the art and hybridomas expressing PSMA antibodies are readily available as taught by Murphy I (col. 6). Furthermore, the suggestion to make chimeric receptors that target PSMA is also found in the art; Murphy II teaches that PSMA is a useful target for immunological methods of treatment (see col. 3, lines 41-47). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the chimeric receptors of Eshhar to comprise an scFv that binds PSMA. One would have been motivated to make such a modification because PSMA has been taught to be a cancer antigen and a target for immune system therapies.

7. Claims 1-4, 6, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al

("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Darcy et al (Darcy, P.K. et al., Eur. J. Immunol. 28: 1663-1672, 1998; cited in the IDS).

Claims 1-4, 6 and 17-19 may be interpreted to read on fusion receptors having a connector, where the connector is a CD8 hinge. The combination of Eshhar, Murphy I and Murphy II fails to teach fusion receptors comprising a linker that is a CD8 hinge. However, using the CD8 hinge in a chimeric T cell receptor construct is known in the art as shown by the teachings of Darcy, which teaches a fusion receptor comprising an anti-CEA scFv linked to transmembrane and cytoplasmic regions of the human FcγR chain, with a CD8 hinge in between the scFv and transmembrane and cytoplasmic regions of FcγR chain. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a linker that is a CD8 hinge.

8. Claims 1-4 rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998) and further in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995).

Capon teaches chimeric proteins that comprise an scFv that binds a tumor antigen that is linked to transmembrane domain that is linked to a cytoplasmic domain. Thus, Capon teaches chimeric proteins that comprise a linker between the scFV and the cytoplasmic domain. Capon fails to teach a chimeric protein having an scFv that binds PSMA. However, antibodies to PSMA are known in the art and hybridomas expressing PSMA antibodies are readily available as taught by Murphy I (col. 6). Furthermore, the suggestion to make chimeric receptors that target

PSMA is also found in the art; Murphy II teaches that PSMA is a useful target for immunological methods of treatment (see col. 3, lines 41-47). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the chimeric receptors of Eshhar to comprise an scFv that binds PSMA. One would have been motivated to make such a modification because PSMA has been taught to be a cancer antigen and a target for immune system therapies.

9. Claims 1-4, 6, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Darcy et al (Darcy, P.K. et al., Eur. J. Immunol. 28: 1663-1672, 1998; cited in the IDS).

The combination of Capon, Murphy I and Murphy II fails to teach fusion receptors comprising a linker that is a CD8 hinge. However, using the CD8 hinge in a chimeric T cell receptor construct is known in the art as shown by the teachings of Darcy, which teaches a fusion receptor comprising an anti-CEA scFv linked to transmembrane and cytoplasmic regions of the human FcγR chain, with a CD8 hinge in between the scFv and transmembrane and cytoplasmic regions of FcγR chain. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a linker that is a CD8 hinge.

10. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) or Capon et al (US

5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Alderson et al (Alderson et al, Eur. J. Immunol, 24(9): 2219-2227, 1994; abstract only).

Neither Eshhar nor Capon teaches cytoplasmic domains that are the 4-1BB cytoplasmic domain. However, both Eshhar and Capon teach generally that cytoplasmic domains may be the cytoplasmic domains of T-cell receptors. Alderson teaches that 4-1BB is a T cell receptor and teaches the DNA sequence. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a fusion receptor comprising a 4-1BB cytoplasmic domain. The motivation for using the 4-1BB cytoplasmic domain is found in the teachings of either Eshhar or Capon, which teach that the cytoplasmic domains of T cell receptors are useful in making chimeric T-cell receptors.

11. Claims 1, 5, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995)Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995), in view of Darcy et al (Darcy, P.K. et al., Eur. J. Immunol. 28: 1663-1672, 1998; cited in the IDS), and further in view of Alderson et al (Alderson et al, Eur. J. Immunol, 24(9): 2219-2227, 1994; abstract only).

Neither Eshhar nor Capon teaches cytoplasmic domains that are the 4-1BB cytoplasmic domain. However, both Eshhar and Capon teach generally that cytoplasmic domains may be the

cytoplasmic domains of T-cell receptors. Alderson teaches that 4-1BB is a T cell receptor and teaches the DNA sequence. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a fusion receptor comprising a 4-1BB cytoplasmic domain. The motivation for using the 4-1BB cytoplasmic domain is found in the teachings of either Eshhar or Capon, which teach that the cytoplasmic domains of T cell receptors are useful in making chimeric T-cell receptors.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
February 10, 2003